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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/788,268	JARVIK, JONATHAN W.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 7 January 2008 are acknowledged and the amendments are entered.

Claims 92-102 are examined and are pending in this Office action.

ALL of the rejections in this Office action are reiterated from the previous Office action.

Specification

The following objections are reiterated from the previous Office action:

The disclosure is objected to because of the following informalities:

There are drawings embedded in the specification on pages 31 and 33.

These drawings are partially cut off on the right side of the figure.

Page 8 of the specification has the grammatical inconsistency on line 4, "the codons encoding each amino acid [amino acid] in the sequence."

Page 14, line 8 has the units inconsistency, "A 10 ϕl aliquot…"

Page 17, line 7 has the units inconsistency, "A 10 ϕl aliquot…"

Page 41, line 16 has an ending to a sentence with two periods.

Appropriate correction is required.

It should be noted that the Remarks of the Applicant are technically not fully responsive because they fail to address these objections. Consequently, in the

absence of arguments or amendments to overcome these objections, they are maintained. However, in the interest of advancing prosecution, the application is examined as it stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. 103 Rejection #1:

Claims 92-93, 95, 97, and 100-102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blanc et al. [USPAT 5,891,695; issued 6 April 1999] in view of Weinshilboum et al. [US Patent 5,470,737; issued 28 November 1995].

Claim 92 is drawn to the following:

A method of analyzing a nucleotide, comprising:

a) providing a polynucleotide having homology to a defined DNA sequence;

b) calculating the masses of two or more polypeptides encoded in two or more overlapping reading frames of said defined DNA sequence thereby obtaining a set of predicted mass values;

c) expressing two or more polypeptides from two or more overlapping reading frames of said polynucleotide, thereby creating two or more expressed polypeptides;

d) measuring the masses of said two or more expressed polypeptides, thereby obtaining a set of observed mass values; and

e) comparing said set of predicted mass values to said set of observed mass values.

Claim 100 is further limiting with the additional limitation that comprises purification of the polypeptide prior to measuring its measured peptide mass signature.

Claim 101 is further limiting with the additional limitation of a list of purification methods used to accomplish the method of claim 100.

Claim 102 is further limiting with the additional limitation of a list of possible spectroscopic methods used to execute the methods.

The preamble of claim 92 is taught in the abstract of Blanc et al. as "The invention concerns nucleotide sequences coding for a polypeptide."

Step a) in the method is described in Example 1, column 9, lines 30-62 and Example 6, column 39, lines 45-51. Example 1 is entitled, "Isolation of total DNA of *Streptomyces pristinaespiralis* strain SP92." Example 6 contains the text, "it is possible to subclone DNA fragments containing these genes. These subclonings were performed in order to be able to deduce subsequently the nucleic acid sequence of the

genes identified,…" Consequently, Blanc et al. teaches a polynucleotide having homology to a defined DNA sequence.

Step c) of the above method is described in Blanc et al. Examples 5.1.1.B and 5.1.2 (columns 14 and 15). In example 5.1.1.B, *S. pristinaespiralis* SP92 Pristinamycin IIA Synthase is purified. The example claims that after this procedure, "the enzyme is pure and, in SDS-PAGE electrophoresis, two subunits of molecular weight estimated at 35,000 and 50,000 are detected." [column 15, lines 20-23] According to Example 5.1.2, polypeptide sequences to be examined, SnaA and SnaB, are cleaved from the protein via Edman degradation, and then purified using high performance liquid chromatography (HPLC). Thus, Example 5.1.2 not only describes step c) of the above method, but additionally describes the limitations of instant claims 100 and 101, which claim "purification of the polypeptide" and "high performance liquid chromatography" as methods for accomplishing this task, respectively.

Steps b), d), and e) are described in Blanc et al., column 46, lines 54-58, and 61-65, which state, "Frames 1 and 3 correspond respectively to the proteins SnaA (SEQ ID NO:17) and SnaB (SEQ ID NO:18) isolated above as described in Example 5 and for which the cloning of the genes is detailed in Example 6… …Moreover, the molecular masses calculated from the sequences are comparable to the apparent molecular masses of the proteins SnaA and SnaB, estimates, respectively, in SDS-PAGE as described in Example 5." Thus, the polypeptide sequence has its molecular weight measured and calculated with both results being compared. Since Blanc et al. uses gel

electrophoresis, Claim 102 is additionally described (Claim 102 dictates methods of measurement of polypeptide masses).

However, Blanc et al. does not teach the use of reading frames that overlap.

The patent of Weinshilboum et al. discusses stably transformed cells expressing human thiopurine methyltransferase.

Figure 4 of Weinshilboum et al. illustrates overlapping reading frames of DNA within human colon carcinoma cells. Example 4, specifically, lines 1-25 of column 14 describes the procedure of comparing the predicted and calculated protein molecular mass translated from an open reading frame of the DNA.

The purpose of the invention of Weinshilboum et al. is described in column 2, lines 50-62, which states that the new method provides a rapid, reproducible, and sensitive in vitro assay which is useful to predict the susceptibility of a given compound or drug to TMPT metabolism.

Claim 93 is dependent from claim 92 with the additional limitation of a difference in the polynucleotide sequence due to a mutation or polymorphism.

Column 47, lines 16-24 of Blanc et al. reveal that there is a multiple nucleotide insertion in the polynucleotide:

> Comparison of the sequence of the product of open reading frame no. 2 with the protein sequences contained in the Genpro bank reveals that an internal portion of this protein is 36% homologous with an internal portion of the first open reading frame of the insertion sequence (IS891) of Anabaena… This result suggests that open reading frame no. 2, designated ORF 401, belongs to an insertion sequence, and that there is hence an insertion sequence located between the snaA and snaB genes.

Claim 95 is dependent from claim 92 with the additional limitation of the use of cDNA as the polynucleotide of interest.

Furthermore, this snaA gene is recorded in the sequence listing in column 75 of Blanc et al. as a sequence of cDNA (SEQ ID no:2 in Blanc et al. is snaA).

Claim 97 is dependent from claim 92 with the additional limitation that the expressed polypeptides are expressed in a living cell.

The procedure of claim 92 was accomplished in living cells (i.e. see Example 1 of Blanc et al. in column 9 which shows use of *S. pristinaespiralis*).

It would have been obvious at the time of the instant invention to modify the molecular mass study of Blanc et al. by use of the analysis of TMPT using overlapping reading frames of Weinshilboum et al. where the motivation would have been that applying the method of Blanc et al. to the study of Weinshilboum et al. would have resulted in a more detailed and thorough analysis of *in vitro* assays which would have aided in better comparing the predicted and calculated protein molecular mass translated from overlapping open reading frames of the DNA useful in predicting the susceptibility of a given compound or drug to TMPT metabolism (see, for example, column 2, lines 50-62 of Weinshilboum et al. and example 4 of Weinshilboum et al.)

Response to Arguments:

Applicant's arguments filed 7 January 2008 have been fully considered but they are not persuasive.

With regard to the Blanc et al. reference, applicant is essentially arguing on pages 2-4 that steps a through e of instant claim 92 cannot be taught because the DNA that was used was not a “defined DNA sequence” as required in step a of claim 92. The instant specification does not provide a limiting definition for a "defined DNA sequence." In the remarks filed 7 January 2008, applicant argues that a "defined" DNA sequence is one in which the sequence is known. The DNA sequence being utilized in Blanc et al. is the total genomic DNA from the mycelia of *S. pristinaespiralis*, thus the source of the Blanc’s DNA is known or “defined.” In the absence of a limiting definition in the specification for the term "defined," the claim language is interpreted broadly to encompass a DNA of "known" or “defined” origin. Consequently, the examiner maintains that steps a through e (with the exception of overlapping reading frames) are taught in Blanc et al.

With regard to the Weinshilboum et al. reference, applicant states:

> Examiner asserts that “Figure 4 of Weinshilboum et al. illustrates overlapping reading frames of DNA within human colon carcinoma cells.” However, Weinshilbaum [*sic*] makes no reference to overlapping reading frames. Figure 4 represents a cDNA molecule. The arrows, some of which overlap, represent DNA primers that were used to sequence the cDNA, not overlapping reading frames.

This argument is not persuasive because while the open box in Figure 4 of Weinshilboum et al. illustrates a single OPEN reading frame, OPEN reading frames and

reading frames are two distinct concepts. (OPEN reading frames require a start codon to enable effective translation.) Absent a limiting definition of "reading frames" in the specification, "reading frames" are interpreted broadly to encompass not only OPEN reading frames, but other reading frames as well. Consequently, the primers in Figure 4 of Weinshilboum et al. initiate transcription of DNA and each primer consequently corresponds to its own reading frame of DNA. Since these primer "arrows" overlap (as applicant states above), the reading frames corresponding to the hybridization of each primer overlap as well.

35 U.S.C. 103 Rejection #2:

Claims 98 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blanc et al. in view of Weinshilboum et al. as applied to claims 92-93, 95, 97, and 100-102 above, in further view of Jermutus et al. [Current Opinion in Biotechnology, 1998, volume 9, pages 534-548].

Claim 98 is further limiting wherein expression of the polypeptide is in a cell free system.

Claim 99 limits the types of extracts which could be used in the cell free system.

Blanc et al. and Weinshilboum et al. make obvious the technique of analyzing masses of polypeptides encoded in overlapping reading frames for the purpose of addressing metabolism.

Blanc et al. and Weinshilboum et al. do not teach use of cell free systems for peptide expression.

The article of Jermutus et al., entitled, "Recent advances in producing and selecting functional proteins by using cell-free translation," states in the abstract:

> Prokaryotic and eukaryotic in vitro translation systems have recently become the focus of increasing interest for tackling fundamental questions in biochemistry. Cell free systems can now be used to study the in vitro assembly of membrane proteins and viral particles, rapidly produce and analyze protein mutants, and enlarge the genetic code by incorporating unnatural amino acids. Using in vitro translation systems, display techniques of great potential have been developed for protein selection and evolution. Furthermore progress has been made to efficiently produce proteins in batch or continuous cell-free translation systems and to elucidate the molecular causes of low yield and find possible solutions for this problem.

Jermutus et al. states in the last paragraph of the second column of page 534, "We will focus primarily on the typical translation systems in use today and discuss some of the factor influencing the amount of total protein made. The most efficient cell-free protein synthesis systems are derived from Escherichia coli, rabbit reticulocytes, or wheat germ…"

Consequently, Jermutus et al. teaches expression of proteins in cell free systems for the purpose of understanding the assembly of proteins and viral particles.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the overlapping reading frame studies of Blanc et al. and Weinshilboum et al. by use of the cell free method of Jermutus et al., where the motivation would have been that the cell free system of Jermutus et al. has the advantages listed in the aforementioned abstract (i.e. batch and continuous processing) for more efficient production of proteins [see abstract of Jermutus et al.].

Response to Arguments:

Applicant has no arguments specific to the reference of Jermutus et al. and this obviousness rejection in the Remarks of 7 January 2008.

35 U.S.C. 103 Rejection #3:

Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blanc et al. in view of Weinshilboum et al. as applied to claims 92-93, 95, 97-99, and 100-102 above, in view of Blanc et al. [Journal of Bacteriology, 1995, volume 177, pages 5206-5214]. This second Blanc et al. reference will be referred to as "Blanc et al. (1995)" throughout this Office action.

Claim 94 limits the polypeptide to comprise an exon.

Blanc et al. and Weinshilboum et al. make obvious the technique of analyzing masses of overlapping reading frames for the purpose of addressing metabolism.

Blanc et al. and Weinshilboum et al. do not explicitly teach polypeptides comprising exons.

The sequence submission of Blanc et al (1995) (U21215), confirms the linear relationship between the cDNA and genomic DNA of the regions of interest in the bacteria S. pristinaespiralis (i.e. there are no introns in the open reading frames of the genomic DNA). Consequently, snaA is an exon which codes for the protein SnaA.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the technique of analyzing masses of overlapping reading frames for the purpose of addressing metabolism of Blanc et al. and Weinshilboum et al. by the use of the exons in Blanc et al. (1995) where the motivation

would have been that Blanc et al. (1995) has more detailed structural information on the biomolecules produced from *Streptomyces pristinaespiralis* which adds further data to the knowledge of methods of biosynthesis of streptogramins in Blanc et al. (see page 5213 of Blanc (1995)).

Response to Arguments:

Applicant has no arguments specific to the reference of Blanc et al. (1995) and this obviousness rejection in the Remarks of 7 January 2008.

35 U.S.C. 103 Rejection #4:

Claim 96 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blanc et al. in view of Weinshilboum et al. as applied to claims 92-95, 97-99, and 100-102 above, in further view of Ohlmeyer et al. [PNAS, volume 90, 1993, pages 10922-10926].

Claim 96 limits the polypeptide to comprise an epitope tag.

Blanc et al. and Weinshilboum et al. make obvious the technique of analyzing masses of overlapping reading frames for the purpose of addressing metabolism.

Blanc et al. and Weinshilboum et al. do not explicitly teach epitope tags.

The study of Ohlmeyer et al. investigates complex synthetic libraries indexed with molecular tags. The purpose of the study of Ohlmeyer et al, as discussed in the last paragraph of column 2 on page 10922, is that the molecular tags allow rapid identification of chemicals in chemical libraries and enable the construction of complex chemical libraries. As an example of the types of tags employed, the paragraph

bridging columns 1 and 2 of page 10924 utilizes epitope tags to identify sequences in an array.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the technique of analyzing masses of overlapping reading frames for the purpose of addressing metabolism of Blanc et al. and Weinshilboum et al. by the use of the epitope tags of Ohlmeyer et al. where the motivation would have been the epitope tags allow for more rapid identification of members of complex synthetic libraries [last paragraph of column 2 on page 10922] for further analysis [such as the molecular weight analysis in Blanc et al. and Weinshilboum et al.]

Response to Arguments:

Applicant has no arguments specific to the reference of Ohlmeyer and this obviousness rejection in the Remarks of 7 January 2008.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center

(EBC) at 866-217-9197 (toll-free).

/RSN/
8 April 2008

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631